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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/870,762	06/06/1997	BRADFORD J. DUFT	030639.0044.~~UTL~~ CPA2	7328

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EXAMINER
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ART UNIT	PAPER NUMBER
1645	33

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
08/870,762	Duft et al.
Examiner	**Art Unit**
S. Devi, Ph.D.	1645

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Mar 18, 2002*

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-6* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-6* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Continued Prosecution Application

1) The request filed on 03/18/2002 (paper no. 30) for a Continued Prosecution Application (C.P.A) under 37 C.F.R 1.53(d) based on parent Application, SN 08/870,762, is acceptable and a C.P.A has been established. It is noted that no preliminary amendment or any response has been submitted along with the request for filing the C.P.A. An action on the C.P.A follows.

Status of Claims

2) No claims have been amended.

Claims 1-6 are pending in the instant application and are under examination.

Prior Citation of Title 35 Sections

3) The text of those sections of Title 35 U.S. Code not included in this action can be found in a prior Office Action.

Prior Citation of References

4) The references cited or used as prior art in support of one or more rejections in the instant Office Action and not included on an attached form PTO-892 or form PTO-1449 have been previously cited and made of record.

Objection(s) to Specification

5) The instant specification is objected to for the following reasons:

(a) The attempt to incorporate subject matter into this application by reference to an international application, WPI Acc. No. 93-182488/22 on page 14, lines 10 and 26 of the instant specification is improper, because the contents of the foreign application appear to be essential material for the instant invention. Applicants are required to amend the disclosure to include the material incorporated by reference. The amendment must be accompanied by an affidavit or declaration executed by the Applicant, or a practitioner representing the Applicant, stating that the amendatory material consists of the same material incorporated by reference in the referencing application. See *In re Hawkins*, 486 F.2d 569, 179 USPQ 157 (CCPA 1973); *In re Hawkins*, 486 F.2d 579, 179 USPQ 163 (CCPA 1973); and *In re Hawkins*, 486 F.2d 577, 179 USPQ 167 (CCPA 1973).

(b) The specification recites abbreviated terms, such as, "ED_{50}" (see page 40, line 18 and page 39, last line); "$ED_{50}S$" (see page 39, line 10); and "IC_{50}" (see page 37, line 17). It is unclear what do these terms stand for or mean.

(c) The use of trademarks in the instant specification has been noted in this application. For example, see page 35, line 22: "Humulin-R"; page 27, line 14: "Triton"; page 27, line 12: "Tween"; page 24, line 6 "Bio-Ion 20"; page 23, line: "Delta Prep 3000". The recitation(s) should be capitalized wherever it appears and be accompanied by the generic terminology. Each letter of the trademark must be capitalized. See M.P.E.P 608.01(V) and Appendix l. Although the use of trademarks is permissible in patent applications, the propriety nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks. It is suggested that Applicants examine the whole specification to make similar corrections to the trademarks, wherever such recitations appear.

Rejection(s) Withdrawn

6) The rejection of claims 1-3 made in paragraph 11 of the Office Action mailed 11/13/00 (paper no. 21) under 35 U.S.C § 103(a) as being unpatentable over Rink *et al.* (US 5,739,106, already of record) ('106) and maintained in paragraph 7 of the Office Action mailed 12/18/01 (paper no. 28), is withdrawn.

Rejection(s) Maintained

7) The rejection of claims 5 and 6 made in paragraph 13 of the Office Action mailed 11/13/00 (paper no. 21) under 35 U.S.C § 103(a) as being unpatentable over Arnelo *et al.* (Arnelo *et al. Am. J. Physiol.* 271: 6 pt 2: R1654-R1659, December 1996) (Arnelo *et al.* I), or Arnelo *et al.* (*Scand. J. Gastroenterol.* 31: 83-89, January 1996) (Arnelo *et al.* II) as applied to claims 4 and 1, and further in view of Bennett *et al.* (US 5,955,443) and maintained in paragraph 8 of the Office Action mailed 12/18/01 (paper no. 28), is maintained for reasons set forth therein.

8) The rejection of claims 1-6 made in paragraph 14 of the Office Action mailed 11/13/00 (paper no. 21) under 35 U.S.C § 103(a) as being unpatentable over Kolterman *et al.* (WO 96/40220, already of record) (Kolterman *et al.*, II) in view of Meglasson (US 5,134,164) and maintained in paragraph 9 of the Office Action mailed 12/18/01 (paper no. 28), is maintained for

reasons set forth therein.

9) The provisional rejection of instant claims (claims 1-6) made in paragraph 10 of the Office Action mailed 11/13/00 (paper no. 21) under the judicially created doctrine of double patenting over the claims (claims 1-15) of the pending application, SN 09/445,517, is maintained for reasons set forth therein. Applicants have requested that this provisional rejection be held in abeyance until the official notification of allowance in the instant or the co-pending application.

Rejection(s) under Double Patenting

10) The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970) and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 C.F.R 1.321(c) may be used to overcome an actual or provisional rejection based on a non-statutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 C.F.R 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 C.F.R 3.73(b).

11) Claims 1-6 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-25 of the U.S. Patent US 6,114,304 (Kolterman *et al.*) in view of Weintraub *et al.* (*Nutrition Rev.* 49: 237-249, 1989) and Robert *et al.* (WO 91/16917). Although the conflicting claims are not identical, they are not patentably distinct from each other, because of the overlapping scope. Instant claims are interpreted in light of the specification. The specification defines "treating" obesity to include "controlling weight", that is "to control body weight" (see page 13). The instant specification also defines "treating" obesity

to include the administration of amylin or amylin agonist to include "the inhibition of weight gain and inducing weight loss" and to alleviate "the symptoms or complications" (see last paragraph on page 13). One of the parameters described in the instant specification to determine amylin agonistic activity is inhibition or delaying of gastric emptying (see page 20; and Examples 7 and 8). That Kolterman's ('304) method of "delaying gastric emptying in a mammal" comprising administering a therapeutically effective amount of an amylin, amylin agonist, i.e., amylin agonist analogue, including $^{25, 28, 29}$pro-h-amylin, encompasses the subject matter of the instant claims is implicit in light of what is known in the art.

That the induction of slowing or delaying of gastric emptying has a direct therapeutic effect on the clinical condition of obesity is well known in the art. For instance, Robert *et al.* demonstrated that a gastric emptying-retarding compound also served as an anti-obesity agent by retaining the food in the stomach of the treated individuals for prolonged periods of time, thus causing no desire to eat, thereby causing weight loss. See page 2, lines 24-26 of Robert *et al.* Weintraub *et al.* expressly teach, slowing of gastric emptying by increasing gastric distension to inhibit food intake, as an approach for treating obesity (see title; and page 43, left column, second full paragraph). Given the Robert's express teaching that a gastric emptying-retarding compound also served as an anti-obesity agent by retaining the food in the stomach of the treated individuals for prolonged periods of time, thus causing no desire to eat, thereby causing weight loss, it would have been obvious to one of ordinary skill in the art at the time the invention was made to use Kolterman's ('304) method comprising administering amylin, an amylin agonist analogue, or an amylin agonist compound, such as, $^{25, 28, 29}$pro-h-amylin, to a human subject for treating obesity to produce the instantly claimed method, with a reasonable expectation of success, because Weintraub *et al.* expressly teach slowing of gastric emptying as an approach for treating obesity.

Rejection(s) under 35 U.S.C. § 112, First Paragraph

12) Claims 1-6 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 1 includes the limitation: "anti-obesity agent" (see lines 2 and 3). However, there

appears to be no descriptive support in the instant specification for this limitation. Instead, the paragraph bridging pages 7 and 8 of the specification describes a composition as follows: Therefore, the new limitation in the base claim is considered to be new matter. *In re Rasmussen*, 650 F2d 1212 (CCPA, 1981). New matter includes not only the addition of wholly unsupported subject matter but also, adding specific percentages or compounds after a broader original disclosure, or even omission of a step from a method. See M.P.E.P. 608.04 to 608.04(c).

Applicants are invited to point to the descriptive support in specific part(s) of the disclosure, as originally filed, for the limitation identified above, or to remove the new matter from the claim(s).

Rejection(s) under 35 U.S.C. § 112, Second Paragraph

13) The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude one or more claims particularly pointing out and distinctly claiming the subject matter which the Applicant regards as his/her invention.

14) Claims 1-6 are rejected under 35 U.S.C § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

(a) Claim 1 is vague and indefinite in the recitation: "an effective amount of a composition" (see line 2), because the limitation "effective" is a relative term which renders the claim indefinite. The limitation "effective" is not specifically defined by the claim, the specification does not provide a standard for ascertaining the requisite degree of effectiveness, and one of ordinary skill in the art would not be able to reasonably envisage the scope of the invention. Whether or not the recited 'amount' encompasses therapeutically effective amount, prophylactically effective amount, pharmacologically effective amount or immunologically effective amount, is not understood. Clarification/correction is requested.

(b) Claims 2-6, which depend directly or indirectly from claim 1, are also rejected under 35 U.S.C. § 112, second paragraph, as being indefinite, because of the indefiniteness identified above in the base claim.

Rejection(s) under 35 U.S.C. § 102

15) The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form

the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

16) Claims 1-6 are rejected under 35 U.S.C § 102(a) as being anticipated by Thompson *et al.* (*Diabetes* 46: Suppl. 1, page 30A, 0116, 02 May 1997) (Thompson *et al.* May, 1997).

Thompson *et al.* (May, 1997) taught a method of subcutaneous administration of pramlintide, i.e., ^{25,28,29}pro-h-amylin, an analog of human amylin, i.e., an amylin agonist, to patients with type II diabetes requiring insulin, at a dose of 30 or 60 micrograms QID (i.e., four times a day) or TID (i.e., three times a day) for a period of four weeks. The method carried out at a pramlintide dose of 60 micrograms TID or QID not only improved glycaemic control in these patients, but also decreased body weight (see abstract), and therefore served as a method of treating obesity.

Claims 1-6 are anticipated by Thompson *et al.* (May, 1997).

17) Claims 1-3 are rejected under 35 U.S.C § 102(b) as being anticipated by MacDonald *et al.* (*Diabetologia* 38: Suppl. 1, A118, August 1995, Applicants' IDS) as evidenced by Robert *et al.* (WO 91/16917).

It is noted that the method claimed in claims 1-6 encompass both insulin-taking and non-insulin-taking human subjects. The method of claims 1-5 does not require that a specific amount of the recited amylin or amylin agonist be administered. The method of claims 1-3 does not require that the recited amylin or amylin agonist be administered via a specific route. Claims 1-4 encompass methods of administering the recited amylin or amylin agonist for a period of hours, days, weeks or months. Claims 1-3 encompass administration of any amylin or amylin agonist by any route, in any quantity and any number of times per day to any human subject for any length of time.

It is further noted that the limitation "treating" obesity is defined in the instant specification to include "controlling weight for cosmetic purposes in humans, that is to control body weight to improve bodily appearance", or preventing "the onset of symptoms or

complications, alleviating the symptoms or complications". See last paragraph on page 13.

The specification at page 11 characterizes 'increased appetite' as a sign strongly associated with obesity (see second paragraph). Thus, increased appetite and therefore, increased food intake is a symptom of obesity and plays an important role in obesity.

It is also noted that one of the parameters described in the instant specification to determine amylin agonistic activity is inhibition or delaying of gastric emptying (see second paragraph on page 20; and Examples 7 and 8). The Office views inhibition or delaying of gastric emptying as an inherent amylin agonistic, body-weight reducing function of pramlintide.

MacDonald *et al.* teach the intravenous infusion of 125 micrograms of human amylin analogue or amylin agonist, AC137, to human subjects with insulin-dependent diabetes mellitus or IDDM who are on insulin. The method induced delayed gastric emptying to such an extent that t50 values could not be calculated for solid or liquid meal components (see abstract).

That the prior method necessarily serves as a method of treating obesity, i.e., "controlling weight for cosmetic purposes in humans, that is to control body weight to improve bodily appearance", or preventing the "onset of symptoms or complications, alleviating the symptoms or complications", is inherent from the teachings of MacDonald *et al.* in light of what is well known in the art. It is inherent that by significantly delaying gastric emptying in the treated patients, the pramlintide used in MacDonald's method necessarily induces weight-controlling or weight-reducing effects and symptom-alleviating effects, since it was well known in the art that anti-gastric emptying agents also served as weight-reducing agents. For instance, Robert *et al.* demonstrated that a gastric emptying-retarding compound also served as an anti-obesity agent by retaining the food in the stomach of the treated individuals for prolonged periods of time, thus causing no desire to eat, thereby causing weight loss. See page 2, lines 24-26 Robert *et al.*

The teachings of MacDonald *et al.* anticipate the instant claims. Robert *et al.* is **not** used as a secondary reference in combination with MacDonald *et al.*, but rather is used to show that every element of the claimed subject matter is disclosed by MacDonald *et al.* (April, 1997). See *In re Samour* 197 USPQ 1 (CCPA 1978).

Claims 1-3 are anticipated by MacDonald *et al.*

18) Claims 1-6 are rejected under 35 U.S.C § 102(a) as being anticipated by Thompson *et al.*

(*Diabetes* 46: 632-636, April 1997, already of record) (Thompson *et al.*, April, 1997) as evidenced by Guthrie *et al.* (US 4,443,619).

It is noted that the instant specification defines "treating" obesity as follows (see page 13):

> ..... the management and care of a patient for the purpose of combating the disease, condition or disorder, and includes the administration of an amylin or an amylin agonist to prevent the **onset of symptoms or complications, alleviating the symptoms or complications**, or eliminating the disease condition or disorder. Treating or preventing obesity therefor includes the inhibition of weight gain and inducing weight loss in patients in need thereof. Additionally, treating or preventing obesity is meant to include **controlling weight for cosmetic purposes in humans, that is to control body weight to improve bodily appearance.** [Emphasis added].

It is noted that the method claimed in claims 1-6 encompass both insulin-taking and non-insulin-taking human subjects. The method of claims 1-5 does not require that a specific amount of the recited amylin or amylin agonist be administered. The method of claims 1-3 does not require that the recited amylin or amylin agonist be administered via a specific route. Claims 1-6 encompass methods of administering the recited amylin or amylin agonist for a period of hours, days, weeks or months. Claims 1-3 encompass administration of any amylin or amylin agonist by any route, in any quantity and any number of times per day to any human subject for any length of time.

It is further noted that the limitation "treating" obesity is defined in the instant specification to include "controlling weight for cosmetic purposes in humans, that is to control body weight to improve bodily appearance", or preventing "the onset of symptoms or complications, alleviating the symptoms or complications". See last paragraph on page 13.

The specification at page 11 characterizes 'increased appetite' as a sign strongly associated with obesity (see second paragraph). Thus, increased appetite and therefore increased food intake is a symptom of obesity and plays an important role in obesity.

It is noted that one of the parameters described in the instant specification to determine amylin agonistic activity is inhibition or delaying of gastric emptying (see second paragraph on page 20; and Examples 7 and 8). The Office views inhibition or delaying of gastric emptying as an inherent amylin agonistic body-weight reducing function of pramlintide.

Thompson *et al.* (April, 1997) teach a method of treating human subjects with IDDM or

type 1 diabetes on insulin, by administering subcutaneously 30 or 100 micrograms (which falls in the dose range recited in claim 6) q.i.d. of pramlintide, an amylin agonist analogue which "incorporates proline substitutions at positions 25, 28 and 29 of the amylin molecule", i.e., ^{25,28,29}pro-h-amylin (see abstract; and page 632). The method induced a dose-dependent **anorexia** and nausea in pramlintide-treated patients at 30 micrograms and 100 micrograms doses respectively (see page 635, left column). Thompson *et al.* (April, 1997) teach the modulation of gastric emptying to be responsible for the reduction of glucose concentrations effected by pramlintide, consistent with the art-reported slowed glucose absorption and reduction in postprandial plasma glucose concentrations resulting from slowing of gastric emptying of liquids and solids in patients with IDDM induced by intravenous infusions of pramlintide (see page 636, left column).

That the anorexic and gastric emptying-slowing effects of pramlintide in the prior art method necessarily result in a therapeutic weight loss in the subjects treated, is inherent from the teachings of the prior art, since therapeutic agents with these effects have been successfully served in the art as anti-obesity agents in the treatment of obesity or weight gain. For instance, Guthrie *et al.* taught the treatment of obesity in mammals with the use of anorectic agents that delay gastric emptying (see abstract; and column 2, lines 25-28). Guthrie *et al.* taught that agents exhibiting potent anorectic, i.e., appetite suppressant activity, in mammals are useful in the treatment of obesity (see column 13, last paragraph).

The teachings of Thompson *et al.* (April, 1997) anticipate the instant claims. Guthrie *et al.* is **not** used as a secondary reference in combination with Thompson *et al.* (April, 1997), but rather is used to show that every element of the claimed subject matter is disclosed by Thompson *et al.* (April, 1997). See *In re Samour* 197 USPQ 1 (CCPA 1978).

Claims 1-6 are anticipated by Thompson *et al.* (April, 1997).

19) Claims 1-6 are rejected under 35 U.S.C. § 102(b) as being anticipated by Kolterman *et al.* (*Diabetologia* 39: 492-499, April, 1996, already of record) (Kolterman *et al.*, 1996) in light of *The Random House Dictionary* (Ed. Flexner *et al.*, Random House, page 32, New York, 1984).

It is noted that the method claimed in claims 1-6 encompass both insulin-taking and non-insulin-taking human subjects. The method of claims 1-5 does not require that a specific amount

of the recited amylin or amylin agonist be administered. The method of claims 1-3 does not require that the recited amylin or amylin agonist be administered via a specific route. Claims 1-6 encompass a method of administering the recited amylin or amylin agonist for a period of hours, days, weeks or months.

It is further noted that the limitation "treating obesity"is defined in the instant specification to include "controlling weight for cosmetic purposes in humans, that is to control body weight to improve bodily appearance", or preventing "the onset of symptoms or complications, alleviating the symptoms or complications". See last paragraph on page 13.

The specification at page 11 characterizes 'increased appetite' as a sign strongly associated with obesity (see second paragraph). Thus, increased appetite and therefore increased food intake are symptoms of obesity and plays an important role a role in obesity.

One of the parameters described in the instant specification to determine amylin agonistic activity is inhibition or delaying of gastric emptying (see second paragraph on page 20; and Examples 7 and 8). Inhibition or delaying of gastric emptying is viewed as an inherent, amylin agonistic anti-obesity function of pramlintide.

Kolterman *et al.* (1996) teach a method of subcutaneous administration of 30, 100 or 300 μg of pramlintide or AC137 (i.e., ^{25,28,29}pro-h-amylin), a human amylin analogue, to human patients with insulin-dependent diabetes mellitus or IDDM who are on insulin. Pramlintide is administered three times daily for a period of 14 days (see abstract; and page 493). This pramlintide administration to insulin-taking IDDM patients induced **anorexia**, recurrent nausea and significant reduction in postprandial hyperglycemia (see paragraph bridging left and right columns on page 497; and third full paragraph, right column on page 498). It is taught that amylin exerts a potent effect which slows gastric emptying in man and can reduce postprandial plasma glucose excursions (see page 493). Kolterman *et al.* (1996) discuss the art-reported accelerated gastric emptying in IDDM patients and suggest that the effect of pramlintide on postprandial plasma glucose concentrations may be predominantly mediated via effects upon gastric emptying (see page 498).

It is noted that the term "anorexia" is defined in '*The Random House Dictionary*' as 'abnormal lack of appetite' (see page 32).

That the prior method necessarily serves as a method of treating obesity, i.e., "controlling weight for cosmetic purposes in humans, that is to control body weight to improve bodily appearance", or preventing the "onset of symptoms or complications, alleviating the symptoms or complications", is inherent from the teachings of Kolterman *et al.* (1996). It is inherent that by inducing anorexia and recurrent nausea, pramlintide used in Kolterman's method necessarily induces abnormal lack of appetite, thereby decreasing if not inhibiting, the food intake, or the quantity or frequency of food intake, which in turn 'controls' the body weight of the patients for cosmetic purposes or 'improves' the bodily appearance of the patients administered with pramlintide.

Claims 1-6 are anticipated by Kolterman *et al.* (Kolterman *et al.*, 1996).

20) Claims 1-6 are rejected under 35 U.S.C § 102(b) as being anticipated by Kolterman *et al.* (WO 95/07098).

It is noted that the instant specification defines "treating" as follows (see page 13):

> ..... the management and care of a patient for the purpose of combating the disease, condition or disorder, and includes the administration of an amylin or an amylin agonist to prevent the onset of symptoms or complications, alleviating the symptoms or complications, or eliminating the disease condition or disorder. Treating or preventing obesity therefor includes the inhibition of weight gain and inducing weight loss in patients in need thereof. Additionally, treating or preventing obesity is meant to include **controlling weight for cosmetic purposes in humans**, that is **to control body weight to improve bodily appearance**. [Emphasis added].

Kolterman *et al.* ('098) teach a method comprising administering a therapeutically effective amount of an amylin, amylin agonist or amylin agonist analogue, such as, ^{25,28,29}pro-h-amylin or AC-0137 or tripro-amylin. The method results in reductio in post-prandial glucose levels and delaying of gastric emptying. Human IDDM patients, who were on insulin therapy, were administered intravenously or subcutaneously with 30, 100 or 300 micrograms of tripro-amylin three times a day for 14 days (see claims 1-3, 19 and 23-26; page 44, last paragraph through page 46, fist full paragraph; page 38 and 39; the full paragraph on page 37; page 21; Figure 11-13 and Examples 2-4). That the prior art method serves necessarily as a method of treating obesity or controlling body weight is inherent from the teachings of Kolterman *et al.* ('098). The Kolterman's ('098) method meets the instantly claimed method with regard to the composition used, the dose and frequency of the composition used, and the subject species

(human) to whom the composition is administered. Therefore, the prior art method inherently and necessarily brings about the same therapeutic effects brought about by the Applicants' method, i.e., controlling weight for cosmetic purposes, or controlling body weight to improve bodily appearance in humans.

Claims 1-6 are anticipated by Kolterman *et al.* ('098).

Rejection(s) under 35 U.S.C. § 103

21) Claims 1-6 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Kolterman *et al.* (*Diabetologia* 39: 492-499, April 1996, already of record) (Kolterman *et al.*, 1996) in view of Robert *et al.* (WO 91/16917).

It is noted that the instant specification defines "treating" as follows (see page 13):

> ..... the management and care of a patient for the purpose of combating the disease, condition or disorder, and includes the administration of an amylin or an amylin agonist to prevent the onset of symptoms or complications, alleviating the symptoms or complications, or eliminating the disease condition or disorder. Treating or preventing obesity therefor includes the inhibition of weight gain and inducing weight loss in patients in need thereof. Additionally, treating or preventing obesity is meant to include **controlling weight for cosmetic purposes in humans**, that is **to control body weight to improve bodily appearance**. [Emphasis added].

It is noted that the method claimed in claims 1-6 encompass both insulin-taking and non-insulin-taking human subjects. The method of claims 1-5 does not require that a specific amount of the recited amylin or amylin agonist be administered. The method of claims 1-3 does not require that the recited amylin or amylin agonist be administered via a specific route. Claims 1-6 encompass methods of administering the recited amylin or amylin agonist for a period of hours, days, weeks or months.

It is further noted that the limitation "treating obesity"is defined in the instant specification to include "controlling weight for cosmetic purposes in humans, that is to control body weight to improve bodily appearance", or preventing "the onset of symptoms or complications, alleviating the symptoms or complications". See page 13 of the instant specification.

The specification at page 11 characterizes 'increased appetite' as a sign strongly associated with obesity. Thus, increased appetite or increased food intake is a symptom of obesity and plays an important role in obesity.

One of the parameters described in the instant specification to determine amylin agonistic

activity is inhibition or delaying of gastric emptying (see page 20; and Examples 7 and 8). Inhibition or delaying of gastric emptying is viewed as an inherent, amylin agonistic, anti-obesity function of pramlintide.

The teachings of Kolterman *et al.* (1996) are explained above. Although Kolterman *et al.* (1996) are silent about the body weight of the human subjects following pramlintide treatment, it is implicit from Kolterman's (1996) teaching that their method necessarily served as a method of treating obesity or inducing weight loss, i.e., a method that 'controls body weight' for cosmetic purposes, or improves bodily appearance as defined in the instant specification, in light of what is known in the art. By significantly delaying/restoring gastric emptying in the treated patients, the pramlintide used in Kolterman's (1996) method necessarily induced weight-controlling or weight-reducing effects, since it is well known in the art that anti-gastric emptying agents also serve as weight-reducing agents. For instance, Robert *et al.* demonstrated that a gastric emptying-retarding compound also served as an anti-obesity agent by retaining the food in the stomach of the treated individuals for prolonged periods of time, thus causing no desire to eat, thereby causing weight loss. See page 2, lines 24-26 of Robert *et al.* Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made that Kolterman's (1996) method also served as a method of treating obesity, i.e., a method of "controlling weight for cosmetic purposes in humans, that is to control body weight to improve bodily appearance", or preventing or alleviating the onset of the symptom of increased appetite or food intake.

Claims 1-6 are *prima facie* obvious over the prior art of record.

22) Claims 1-6 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Kolterman *et al.* (*Diabetologia* 39: 492-499, April, 1996, already of record) (Kolterman *et al.*, 1996) or Kolterman *et al.* (WO 95/07098) ('098) in view of Frishman *et al.* (*In*: *Cardiovascular Pharmacotherapeutics*. (Eds) Frishman WH *et al.* McGraw-Hill Health Professions Division, New York, Chapter 48, pages 1093-1114, February 1997), or Weintraub *et al.* (*Nutrition Rev.* 49: 237-249, 1989).

It is noted that the instant specification defines "treating" as follows (see page 13):

> ..... the management and care of a patient for the purpose of combating the disease, condition or disorder, and includes the administration of an amylin or an amylin agonist to prevent the onset of symptoms or complications, alleviating the symptoms or complications, or eliminating the disease condition or disorder.

> Treating or preventing obesity therefor includes the inhibition of weight gain and inducing weight loss in patients in need thereof. Additionally, treating or preventing obesity is meant to include **controlling weight for cosmetic purposes in humans**, that is **to control body weight to improve bodily appearance.** [Emphasis added].

The teachings of Kolterman *et al.* (1996) or Kolterman *et al.* ('098) have been explained above, which are silent about the control of body weight of the human subjects following treatment with pramlintide, i.e, an amylin species, and therefore silent about the use of their method for treating obesity, i.e., to control body weight for cosmetic purposes, or to improve bodily appearance.

However, Frishman *et al.* taught amylin to have anorectic effect (see page 1106, right column, last paragraph). Frishman *et al.* expressly taught the use of peripherally acting amylin as one of the innovative strategies to treat obesity (see Table 48-3). It is further taught that the administration of amylin both centrally and peripherally reduces food intake. Frishman *et al.* also taught that amylin was equally effective in decreasing feeding in ob/ob and db/db mice (see page 1107, left column, lines 1 and 2).

Weintraub *et al.* expressly teach, slowing of gastric emptying by increasing gastric distension to inhibit food intake, as an approach for treating obesity (see title; and page 43, left column, second full paragraph).

Given that Kolterman's (1996) method induces both anorexia and delay in gastric emptying in human patients, or given that Kolterman's ('098) method results in delaying of gastric emptying, it would have been obvious to one of ordinary skill in the art at the time the invention was made to use Kolterman's (1996 or '098) method of subcutaneous administration of pramlintide for treating obesity, i.e., controlling body weight for cosmetic purposes, or controlling body weight to improve bodily appearance, to produce the instant invention, with a reasonable expectation of success. One skilled in the art would have been motivated to produce the instant invention for the expected benefit of using Kolterman's (1996 or '098) method, not only to treat IDDM, but advantageously, for treating obesity as well, by making use of the anorectic and/or the anti-gastric emptying properties of Kolterman's (1996 or '098) pramlintide, since Frishman *et al.* expressly provides the motivation by teaching the use of peripherally acting amylin as one of the

innovative strategies to treat obesity, or since Weintraub *et al.* expressly teach slowing of gastric emptying as an approach for treating obesity.

Claims 1-6 are *prima facie* obvious over the prior art of record.

23) Claims 1-3 are rejected under 35 U.S.C § 103(a) as being unpatentable over Kong *et al.* (*Diabetologia* 40: 82-88, January 1997, Applicants' IDS) (Kong *et al.*, 1997), or MacDonald *et al.* (*Diabetologia* 38: Suppl. 1, A118, August 1995, Applicants' IDS) in view of Robert *et al.* (WO 91/16917) and Jonderko *et al.* (*Aliment. Pharmacol. Ther.* 5: 413-418, 1991) (Jonderko *et al.*, 1991) and Frishman *et al.* (*In*: *Cardiovascular Pharmacotherapeutics*. (Eds) Frishman WH *et al.* McGraw-Hill Health Professions Division, New York, Chapter 48, pages 1093-1114, February 1997) or Morley *et al.* (*Pharmacol. Biochem. Behav.* 44: 577-580, 1993) (Morley *et al.*, 1993).

The teachings of MacDonald *et al.* are explained above.

Kong *et al.* (1997) teach a method of intravenous infusion of 125 micrograms (i.e., an effective amount) of pramlintide, an amylin species, to human subjects with IDDM or type 1 diabetes mellitus. The method delayed gastric emptying so much that t50 values could not be calculated for solid or liquid meal components (see abstract; page 85 and Figure 3). Kong *et al.* (1997) teach that faster rates of gastric emptying have been reported in humans with IDDM and that slowing the rate of gastroenteritis in these patients might prove beneficial in improving glycaemic control. Kong *et al.* (1997) conclude that amylin or an amylin agonist may be useful in modifying gastric emptying. Kong *et al.* (1997) specifically recommend amylin or amylin agonist for IDDM or type 1 patients having rapid gastric emptying (see page 87, right column). Although Kong *et al.* or MacDonald *et al.* are silent about the change in body weight of the human subjects following pramlintide treatment, it is implicit from Kong's or MacDonald's teaching that their method necessarily served as a method of treating obesity or inducing weight loss, i.e., a method of 'controlling body weight' for cosmetic purposes, or improving bodily appearance, in light of what is known in the art.

It was known in the art that gastric emptying-retarding compounds also serve as anti-obesity agents. For instance, Robert *et al.* demonstrated that a gastric emptying-retarding compound also served as an anti-obesity agent by retaining the food in the stomach of the treated individuals for prolonged periods of time, thus causing no desire to eat, thereby causing weight

loss. See page 2, lines 24-26 of Robert *et al.*

Frishman *et al.* taught amylin to have anorectic effect (see page 1106, right column, last paragraph). Frishman *et al.* expressly taught the use of peripherally acting amylin as one of the innovative strategies to treat obesity (see Table 48-3). It is taught that the administration of amylin both centrally and peripherally reduces food intake. Frishman *et al.* also taught that amylin was equally effective in decreasing feeding in ob/ob and db/db mice (see page 1107, left column, lines 1 and 2).

Similarly, Morley *et al.* (1993) showed that amylin is a peripheral anorectic peptide. Morley *et al.* (1993) taught that administration of amylin to a mammal decreased or suppressed food intake (see abstract).

Jonderko *et al.* (1991) teach that gastric emptying rate influences the feeling of satiety. Jonderko *et al.* expressly teach that the combination of an anorectic effect with the inhibition of gastric emptying can be considered a desirable feature of an anti-obesity agent (see page 416, first sentence under 'Discussion').

Given the art-demonstrated anti-gastric emptying function and the peripheral anorectic function of amylin as taught by Kong *et al.* and Frishman *et al.* or Morley *et al.* respectively, it would have been obvious to one of ordinary skill in the art at the time the invention was made to use Kong's or MacDonald's method of administration of pramlintide for treating obesity, i.e., controlling body weight for cosmetic purposes, or controlling body weight to improve bodily appearance, to produce the instant invention, with a reasonable expectation of success, because Robert *et al.* expressly taught that a gastric emptying-retarding compound also served as an anti-obesity agent by retaining the food in the stomach of the treated individuals for prolonged periods of time, thus causing no desire to eat, thereby causing weight loss. One skilled in the art would have been motivated to produce the instant invention for the expected benefit of using Kong's (1997) or MacDonald's method, not only to treat IDDM, but advantageously, for treating obesity as well by making use of the anorectic and anti-gastric emptying properties of Kong's (1997) or MacDonald's amylin species, since amylin, advantageously, possesses the combination of the anorectic and the anti-gastric emptying properties, the two properties desirable in an anti-obesity agent as taught by Jonderko *et al.* (1991).

Claims 1-3 are *prima facie* obvious over the prior art of record.

24) Claims 1-6 are rejected under 35 U.S.C § 103(a) as being unpatentable over Kolterman *et al.* (WO 95/07098) ('098) or Kolterman *et al.* (*Diabetologia* 39: 492-499, April, 1996, already of record) (Kolterman *et al.*, 1996) in view of Morley *et al.* (*Pharmacol. Biochem. Behav.* 44: 577-580, 1993) (Morley *et al.*, 1993) and Jonderko *et al.* (*Aliment. Pharmacol. Ther.* 5: 413-418, 1991) (Jonderko *et al.*, 1991).

It is noted that the instant specification defines "treating" as follows (see page 13):

> ..... the management and care of a patient for the purpose of combating the disease, condition or disorder, and includes the administration of an amylin or an amylin agonist to prevent the onset of symptoms or complications, **alleviating the symptoms** or **complications**, or eliminating the disease condition or disorder. Treating or preventing obesity therefor includes the inhibition of weight gain and inducing weight loss in patients in need thereof. Additionally, treating or preventing obesity is meant to include **controlling weight for cosmetic purposes in humans**, that is **to control body weight to improve bodily appearance**. [Emphasis added].

Kolterman *et al.* ('098) teach a method comprising administering a therapeutically effective amount of an amylin, amylin agonist or amylin agonist analogue, such as, ^{25,28,29}pro-h-amylin or AC-0137 or tripro-amylin. The method results in reductio in post-prandial glucose levels and delaying of gastric emptying. Human IDDM patients, who were on insulin therapy, were administered intravenously or subcutaneously with 30, 100 or 300 micrograms of tripro-amylin three times a day for 14 days (see claims 1-3, 19 and 23-26; page 44, last paragraph through page 46, fist full paragraph; page 38 and 39; the full paragraph on page 37; page 21; Figure 11-13 and Examples 2-4).

Kolterman *et al.* (1996) teach a method of subcutaneous administration of 30, 100 or 300 μg of pramlintide or AC137 (i.e., ^{25,28,29}pro-h-amylin), a human amylin analogue, to human patients with insulin-dependent diabetes mellitus or IDDM who are on insulin. Pramlintide is administered three times daily for a period of 14 days (see abstract; and page 493). This pramlintide administration to insulin-taking IDDM patients induced **anorexia**, recurrent nausea and significant reduction in postprandial hyperglycemia (see paragraph bridging left and right columns on page 497; and third full paragraph, right column on page 498). It is taught that amylin exerts a potent effect which slows gastric emptying in man and can reduce postprandial plasma glucose excursions (see page 493). Kolterman *et al.* (1996) discuss the art-reported accelerated

gastric emptying in IDDM patients and suggest that the effect of pramlintide on postprandial plasma glucose concentrations may be predominantly mediated via effects upon gastric emptying (see page 498).

Although Kolterman *et al.* ('098 or 1996) do not expressly teach that their method of administration to a human subject, 30, 100 or 300 micrograms of amylin or an amylin agonist such as ^{25,28,29}pro-h-amylin, or an amylin agonist analogue subcutaneously 1-3 times per day treats human obesity, it is implicit that Kolterman's ('098 or 1996) method serves as a method of treating obesity in light of what is well known in the art.

For instance, Jonderko *et al.* (1991) teach that gastric emptying rate influences the feeling of satiety. Jonderko *et al.* expressly teach that the combination of an anorectic effect with the inhibition of gastric emptying can be considered a desirable feature of an anti-obesity agent (see page 416, first sentence under 'Discussion').

Morley *et al.* (1993) showed that amylin is a peripheral anorectic peptide. Morley *et al.* (1993) teach that administration of amylin to a mammal decreased or suppressed food intake (see abstract).

Since amylin is an art-known anorectic agent as taught by Morley *et al.* (1993) and an anti-gastric emptying agent as demonstrated by Kolterman *et al.* ('098 or 1996), it would have been obvious to one of ordinary skill in the art at the time the invention was made to use Kolterman's ('098 or 1996) method of administering to a human subject a composition comprising amylin, an amylin agonist analogue, or an amylin agonist compound, such as, ^{25,28,29}pro-h-amylin, for treating human obesity to produce the instantly claimed method, with a reasonable expectation of success. Since the combination of an anorectic effect and the inhibition of gastric emptying is taught in the art to be a desirable feature in an anti-obesity agent as taught by Jonderko *et al.* (1991), one skilled in the art would have been motivated to produce the instant invention for the expected benefit of treating obesity in humans, as treatment of human obesity is highly desired in the art. Because the amylin used in Kolterman's ('098 or 1996) method beneficially or desirably exerts both an anorectic effect and an anti-gastric emptying effect as taught by Morley *et al.* (1993) and Jonderko *et al.* (1991) respectively, Kolterman's ('098 or 1996) amylin would have been expected to serve effectively as a therapeutic anti-obesity agent in the prior art method. Those skilled in the art

would have understood that Kolterman's ('098 or 1996) method of delaying gastric emptying by amylin administration would have also served as a method of treating obesity. Kolterman's ('098 or 1996) method is viewed as a method that improves bodily appearance and 'controls body weight' for cosmetic purposes.

Claims 1-6 are *prima facie* obvious over the prior art of record.

25) Claims 1-6 are rejected under 35 U.S.C § 103(a) as being unpatentable over Kolterman *et al.* (WO 95/07098) (Kolterman *et al.*, '098) or Kolterman *et al.* (*Diabetologia* 39: 492-499, April, 1996, already of record) (Kolterman *et al.*, 1996) in view of Frishman *et al.* [*In*: *Cardiovascular Pharmacotherapeutics*. (Eds) Frishman WH *et al.* McGraw-Hill Health Professions Division, New York, Chapter 48, pages 1093-1114, February 1997] and Jonderko *et al.* (*Israel J. Med. Sci.* 25: 20-24, 1989) (Jonderko *et al.*, 1989) or Guthrie *et al.* (US 4,443,619).

The disclosure of Kolterman *et al.* ('098 or 1996) has been explained above. A *Graham v. John Deere* factual inquiry indicates that Kolterman *et al.* ('098 or 1996) are silent about their method of administration to a human subject, 30, 100 or 300 micrograms of amylin or an amylin agonist such as ^{25,28,29}pro-h-amylin, or an amylin agonist analogue intravenously or subcutaneously, 1-3 times per day, treats human obesity. However, it is implicit that Kolterman's ('098 or 1996) method serves as a method of treating obesity in light of what is well known in the art.

However, Frishman *et al.* teach the use of peripherally acting amylin as one of the innovative strategies to treat obesity (see Table 48-3). The administration of amylin both centrally and peripherally reduces food intake. Amylin is taught to have anorectic effect (see page 1106, right column, last paragraph). Frishman *et al.* teach that amylin was equally effective in decreasing feeding in ob/ob and db/db mice (see page 1107, left column, lines 1 and 2).

Jonderko *et al.* (1989) expressly suggest that anorectic agents that delay GE or gastric emptying might contribute to progress in the treatment of obesity (see the last sentence in the paragraph bridging pages 22 and 23).

Similarly, Guthrie *et al.* teach that agents exhibiting potent anorectic or appetite suppressant activity in mammals are useful in the treatment of obesity (see column 13, last paragraph). Guthrie *et al.* teach the use of anorectic agents that delay gastric emptying for the

treatment of obesity in mammals (see abstract; and column 2, lines 25-28).

Given that amylin is an art-known peripherally acting anorectic agent, which is known to reduce food intake in mammals as taught by Frishman *et al.* and an anti-gastric emptying and/or anorectic agent as demonstrated by Kolterman *et al.* ('098 or 1996), it would have been obvious to one of ordinary skill in the art at the time the invention was made to use Kolterman's ('098 or 1996) method of administering an amylin, an amylin agonist analogue, or an amylin agonist compound, such as, ^{25,28,29}pro-h-amylin, to a human subject for treating obesity to produce the instantly claimed method, with a reasonable expectation of success. Since anorectic agents that delay gastric emptying are suggested in the art for the treatment of obesity as taught by Jonderko *et al.* (1989) or Guthrie *et al.*, one skilled in the art would have been motivated to produce the instant invention for the expected benefit of treating obesity in humans, as treating human obesity or controlling human body weight is highly desired in the art. Given the knowledge in the art, one skilled in the art would have readily understood that the anti-gastric emptying amylin used in Kolterman's ('098 or 1996) method beneficially or desirably also exerts an anorectic effect as taught by Frishman *et al.* and that Kolterman's ('098 or 1996) amylin would have been expected to serve effectively as a therapeutic anti-obesity agent in the prior art method. Those skilled in the art would have understood that Kolterman's ('098 or 1996) method of delaying gastric emptying by the administration of anorectic amylin would have also served as a method of treating obesity, because Jonderko *et al.* (1989) or Guthrie *et al.* explicitly teach or suggest that anorectic or appetite-suppressing agents that delay gastric emptying are also useful in the treatment of obesity.

Claims 1-6 are *prima facie* obvious over the prior art of record.

Remarks

26) Claims 1-6 stand rejected.

27) The prior art made of record and not currently relied upon in any of the rejections is considered pertinent to Applicants' disclosure:

- Frank *et al.* (*Gastroenterology* 109: 755-765, 1995) teach that gastric emptying of liquids is significantly accelerated in type II diabetes mellitus (see abstract).
- Klein *et al.* (US 5,498,424) teach the use of anorexigenic agents in treating obesity and also advantageously assisting non-obese persons in losing weight (see abstract).

- Cooper *et al.* (US 5,124,314, already of record) suggest amylin to be of clinical utility as an appetite suppressant (see sixth paragraph in column 1).

- Balasubramaniam *et al.* (*Peptides* 12: 919-924, 1991) teach the anorectic effects of and inhibition of food intake by human amylin (see entire document).

- Kolterman *et al.* (*Diabetologia* 39: 492-499, April, 1996, already of record) (Kolterman *et al.*, 1996) acknowledge that based on genetic work, some skilled in the art have referred to amylin as either 'amylin' or 'IAPP' (see page 492, right column).

- Kong *et al.* (*Diabetes* 46: Suppl. 1: 154A, 1997) teach the subcutaneous administration of a single dose of 30, 60 or 90 micrograms of pramlintide in humans with IDDM or type 1 diabetes mellitus on insulin therapy. All three doses of pramlintide delayed gastric emptying of the solid component of the first meal (see abstract).

- Clementi *et al.* (*Experientia* 52: 677-679, 1996) taught that different doses of rat amylin injected centrally or peripherally decreased gastric emptying and intestinal transit in rats. Clementi *et al.* taught that subcutaneous administration of 25, 50 or 100 micrograms per kg of amylin dose-dependent effects (see abstract; Figure 3 and page 679).

- Young *et al.* from Amylin Pharmaceuticals Inc. (*Diabetologia* 38: 642-648, 1995, Applicants' IDS) showed that subcutaneous injection of rat amylin dose-dependently inhibited gastric emptying in both normal and diabetic rats (see page 643). Young *et al.* discuss a prior art study which shows that gastric emptying is accelerated in an animal model of IDDM, a condition of amylin deficiency. Exogenous amylin is taught to potently and dose-dependently inhibit gastric emptying (see page 647).

- Brown *et al.* (*Diabetes* 43: Suppl. 1: 172A, 1994) demonstrated that gastric emptying is slowed by amylin administration in dogs (see abstract).

- Phillips *et al.* (US 5,187,154) expressly teach a method useful in prophylactic treatment of the obese individuals by delaying or inhibiting gastric emptying (see abstract). Phillips *et al.* teach that delaying gastric emptying appears to slow delivery of glucose to the duodenum which reduces postprondial hyperglycemia. Phillips *et al.* teach that in delaying gastric emptying, a treatment is provided to control the development or at least delay the onset of symptoms that are frequently associated with the onset of or have a tendency to develop diabetes

mellitus (see abstract; and column 4, first full paragraph).

- Wright *et al.* (*Gastroenterology* 84: 747-751, 1986) expressly teach that the rate of solid gastric emptying in the obese subjects is abnormally rapid. Wright *et al.* further teach that obese subjects were found to have a more rapid emptying rate than nonobese subjects and that obese men were found to empty much more rapidly than their nonobese counterparts (see abstract).

- Newgard *et al.* (US 6,110,707, filed 17 January 1997) expressly teach a method of providing amylin to a mammal (i.e., inclusive of humans) exhibiting obesity. Newgard *et al.* expressly teach a method of providing amylin to a mammal (i.e., inclusive of humans) exhibiting gastric emptying (see column 4, lines 41-44). Cells encoding amylin are administered to the mammal intraperitoneally or subcutaneously (see column 4, lines 50-52). Newgard *et al.* disclose that amylins may be used in the treatment of obesity (see column 38, lines 2-5).

- Edwards *et al.* (*Life Sci.* 51: 1819-1912, 1992) teach that amylin produces anorexia and that amylin is much mor effective in decreasing food intake when given peripherally than centrally. Edwards *et al.* state that Morley and Flood (*American J. Med.* 81: 679-695, 1986) have demonstrated that amylin decreases food intake in both normal and diabetic mice following parenteral administration. Edwards *et al.* teach that amylin is more effective in reducing food intake in diabetic animals than in non-diabetic animals (see page 1908, under 'Anorexia'). Anorexia is taught to be another effect of amylin (see last paragraph on page 1908).

- Cooper *et al.* (*Biochim. Biophys. Acta* 1014: 247-258, 1989, already of record) teach that NIDDM is associated with obesity in more than 65% of patients suggesting the possibility that this type of diabetes may be due to a disordered mechanism of appetite regulation or energy expenditure (see the sentence bridging pages 255 and 256).

- Carty *et al.* (WO 9637612 and US 6,187,991) disclose a recombinant DNA expressing islet amyloid polypeptide (IAPP) to develop products for use in treatment of obesity and diabetes (see title and abstract).

- De Luca *et al.* (US 4,960,759) teach that intravenous infusion of CCK reduces food intake both in obese and lean human subjects. De Luca *et al.* teach that cholecystokinin (CCK) produces decrease of gastric emptying (see column 1, lines fourth full paragraph).

- More than a year prior to the effective filing date of the instant invention, Young *et al.* from Amylin Pharmaceuticals (*Drug Development Res.* 37: 231-248, 1996, already of record) taught that amylin is absent or reduced in individuals with type I diabetes mellitus **and** "in many insulin-treated patients with type II diabetes". Young *et al.* taught that amylin replacement therapy may be beneficial in amylin-deficient individuals, such as, those with type I diabetes mellitus and with insulin-requiring type II diabetes mellitus (see abstract; and page 231). Among multiple potent actions of exogenously administered amylin, such as, pramlintide, reduction f postprandial hyperglycemia and inhibition of gastric emptying of solids and liquids in type I diabetic subjects, which is believed to be associated with postprandial glucose-smoothing in humans, are the two. Young *et al.* expressly teach that, in humans, "a striking effect" of the human amylin analogue, pramlintide, is "the reduction of postprondial hyperglycemia" in subjects with type I and insulin-treated type II diabetes mellitus (see page 232, left column).

- It is well known in the art that food intake and obesity are closely associated with each other. For instance:

  - Chen *et al.* (US 5,690,691) teach that in an obese person, food is passed from the stomach into the small intestine at a relatively fast rate thereby causing the person to feel hungry and that this encourages additional caloric intake beyond that which is necessary for good health. Chen *et al.* further teach that it could be advantageous to prolong the time food is kept in the obese patient's stomach to promote a prolonged "full" feeling and discourage further food intake (see column 8, second full paragraph).

  - Bogentoft *et al.* (US 5,462,742) teach that the serious problem of obesity could be helped by a reduced food intake and that decreasing energy intake causes weight loss in obese subjects. Bogentoft *et al.* teach that slowing gastric emptying results in these effects (see column 1, lines 29-37).

- Kolterman *et al.* (US 6,114,304) teach that surprisingly, amylin, "previously described as a hyperglycemic agent (i.e., one causing elevated glucose) was found instead to decrease post-prandial plasma glucose levels in dogs (see column 16, lines 53-57).

- Beaumont *et al.* (US 5,321,008) disclose a method comprising administering a therapeutically effective amount of calcitonin, with or without amylin (see abstract; and column 4,

third full paragraph). Calcitonin in an amylin agonist (see column 3, lines 34 and 35 and column 7, third full paragraph). The method is used for treatment of type 1 and type 2 diabetes in humans and other insulin-requiring states (see last two lines in column 4). The therapeutic regimen can be 100 micrograms of amylin alone, or 100 micrograms of calcitonin alone (see column 9, second full paragraph and Table 3). Administration of amylin or calcitonin composition in solution is by subcutaneous route in a pharmaceutically acceptable form (see under 'Composition' in column 12). The subcutaneous administration is in an insulin-requiring human (see column 7, lines 11-14). The method is also effective in achieving improved glycemic control over insulin therapy (see column 3). The therapeutic dosage given varies from 0.1 to 1.0 micrograms and is administered in one or multiple doses (see column 13, first full paragraph).

- Aquino *et al.* (WO 95/28419 and US 5,739,129) disclosed the use of anorectic agents for treating obesity as well as related pathologies, such as, diabetes or hypertension (see entire document).

- Klein *et al.* (US 5,498,424) teach that most pharmacological approaches to the treatment of obesity and methods of weight loss primarily focus on lowering the energy intake of the obese patient and resort to anorectic drugs that modify the metabolism involved in appetite regulation (see column 2, lines 31-36). Keown *et al.* teach that anorexigenic agents are advantageously used to also assist non-obese persons in losing weight (see abstract).

- Wright *et al.* (*Gastroenterology* 84: 747-751, 1983) teach that obese subjects have an abnormally rapid rate of gastric emptying compared to non-obese subjects (see abstract), whereas obese subjects who were able to lose wight did not show significant change in the rates of gastric emptying of solids or liquids (see paragraph bridging left and right columns on page 749). Hunt *et al.* taught that as discussed in the prior art by others, "rapid emptying is a predisposing factor in the genesis of increased food intake and obesity". Hunt *et al.* expressly taught that the "fact that the obese subjects who were able to lose weight effectively have intermediate solid gastric emptying rates" supports the concept.

- Kolterman *et al.* (*Diabetologia* 37: Suppl. 1: A72, 278, 1994) teach a method of delaying gastrointestinal absorption of nutrients and reducing postprandial hyperglycemia in humans with juvenile-onset diabetes by intravenous infusion of 30, 100 or 300 micrograms of tri-

pro amylin (see abstract).

- Lartey *et al.* (US 5,578,579) teach that "delayed gastric emptying" refers to slow evacuation of gastric contents into the small intestine not caused by mechanical obstruction of the gastric outlet. Lartey *et al.* teach that intractable nausea and vomiting may lead to significant weight loss (see fourth paragraph in column 5).

- Young *et al.* (*Diabetes* 45: Suppl.2: page 187A, A689, 1996) teach that amylin is deficient not only in Type I diabetes, but also in some cases of Type II diabetes (see abstract).

28) Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. Papers should be transmitted via the PTO Fax Center located in Crystal Mall 1. The transmission of such papers by facsimile must conform with the notice published in the Official Gazette, 1096 OG 30, November 15, 1989. The CM1 facsimile center's telephone number is (703) 308-4242, which is able to receive transmissions 24 hours a day and 7 days a week. The RightFax number for submission of before-final amendments is (703) 872-9306. The RightFax number for submission of after-final amendments is (703) 872-9307.

29) Any inquiry concerning this communication or earlier communications from the Examiner should be directed to S. Devi, Ph.D., whose telephone number is (703) 308-9347. A message may be left on the Examiner's voice mail system. The Examiner can normally be reached on Monday to Friday from 7.15 a.m. to 4.15 p.m. except one day each bi-week, which would be disclosed on the Examiner's voice mail system.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Lynette Smith, can be reached on (703) 308-3909.

May, 2002

S. DEVI, PH.D.
PRIMARY EXAMINER